REMARKS

I. Preliminary remarks

Claims 21, 23 and 38 are amended herein and claim 22 is canceled. The amendments to the claims are supported throughout the application as filed. The amendment to claim 28 corrects an obvious typographical error that one of skill in the art would recognize. No new matter has been introduced by these amendments.

II. The objection to the claims has been overcome

The Examiner objected to claims 25-28, asserting that each of these dependent claims failed to further limit the subject matter of a previous claim. In particular, the Examiner stated that "[c]laim 1 requires the production of an antigenic peptide. Claims 25-28 require virus and this is not an antigenic peptide. The claims will be treated as if they only recite fragment." Office Action at page 3. In response, Applicant traverses.

In responding to this objection, Applicant will interpret the Examiner's reference to canceled claim 1 as a reference to pending independent claim 21, from which each of claims 25-28 ultimately depend. Additionally, Applicant notes that claim 25 does not recite the term "virus" and is not limited to a viral antigenic polypeptide. For this reason alone, the objection to claim 25 is improper and should be withdrawn.

Under 35 U.S.C. § 112, fourth paragraph, a "claim in dependent form shall be construed to incorporate by reference all the limitations of the claim to which it refers." Claim 26 expressly recites "virus," but that term refers to the source of the antigenic polypeptide (i.e., "wherein the pathogenic organism is a virus or a bacterium"). Claim 26 depends directly from claim 25, and claim 25 recites that "the antigenic polypeptide is an antigen of a pathogenic organism." Thus, the virus is a pathogenic organism providing a source for the antigen, which is an antigenic polypeptide. There is no reasonable basis for concluding that claim 26 requires a virus when claim 26 expressly recites that it is the pathogenic organism that is a virus (or a bacterium) and claim 25, the claim from which claim 26 directly depends, expressly recites that the antigenic polypeptide is an antigen of a pathogenic organism. Combining these observations, claim 26 effectively recites, in pertinent part, that it is drawn to the method of claim 24 wherein the antigenic polypeptide is

an antigen of a pathogenic organism that is a virus (or bacterium). That effective recitation does not require the virus itself, it merely defines the source of the antigenic polypeptide.

Stated in the alternative, the antigenic polypeptide need not be the whole virus, it merely needs to be at least an antigenic region encoded by part of the virus. For example, the specification describes the use of part of the structural glycoproteins E0 and E2 that are incorporated in the lipid envelope of the bovine viral diarrhea virus (BVDV), together with the non-structural protein, NS3. The NS3 protein does not form part of the virus itself, but rather is encoded by the virus RNA to make an enzyme within infected cells that acts as an integral part of the cellular process for making new virus (essential to the replication of the virus). As such, it has no part in making up the actual virus, but merely is a multifunctional protein produced in a host cell that is encoded by the virus RNA. It remains within the cells and is not incorporated into the BVDV virus. Therefore, provided that the polypeptide is antigenic, the method of the present invention does not require the use of whole virus and the dependent claims provide further definition of the antigenic polypeptide in terms of its source. Claims 27 and 28 do not recite "virus" but depend, directly or indirectly, from claim 26 and thereby incorporate the limitations of claim 26, shown above not to require the virus itself.

For the foregoing reasons, Applicant submits that the objection to claims 25-28 has been overcome and should be withdrawn.

III. The rejection of claims 25-28 under 35 U.S.C. § 112, second paragraph, has been overcome

The Examiner rejected claims 25-28 under § 112, second paragraph, asserting that "derived" is undefined. Applicant notes that none of claims 25-28 recites the term "derived" but do recite the term "derivative," and Applicant interprets the rejection as based on the recitation of "derivative" in each of claims 25-28. In response, Applicant traverses.

The person of ordinary skill in the art would be well-acquainted with the term "derivative" and would be familiar with the type of polypeptide encompassed by that term. Any skilled person would consider the term "derivative" to encompass any sequence variation. All pestiviruses (and all Flaviviruses, the Family to which pestiviruses belong) are RNA viruses. As such, all of these viruses are known to be hypervariable, and to collectively exist as an antigenic spectrum, even within a single cell. This has been known in the field of

RNA virology as "quasi species variability" and effectively means that all of the viruses vary in their actual composition from one another.

It would be routine for a person skilled in the art to determine candidate regions of a given antigenic polypeptide that are themselves antigenic. A skilled person would routinely generate and assess such derivatives for antigenicity and, hence, suitability for use in the methods of the invention. Such regions could then be tested using the method of the present invention guided by the teachings in the specification, and in particular in the examples provided therein. Moreover, aware of the variability of pestiviruses, the specification discloses the use of various antigenic polypeptides from more than one virus in terms of both E2 and E0 fragments. Additionally, all of the derivatives of antigenic polypeptides must themselves be antigenic polypeptides.

Under the law, the breadth of a definition for a claim term is not to be equated with indefiniteness. Applicant submits that, while the claims are properly tailored to the scope of the disclosed invention, the Examiner has supported the rejection based on the perceived breadth of the term "derivative," while ignoring the definite and unambiguous meaning of the term as recited in the rejected claims. One of skill in the art would understand that an antigenic polypeptide derivative is an antigenic polypeptide, or a fragment of an antigenic polypeptide, that differs in sequence but retains the property of being antigenic, such as the antigenic polypeptide variants characteristic of the hypervariable polypeptides of many pathogenic organisms, e.g., the pestiviruses.

For the foregoing reasons, Applicant submits that the the term "derivative," as recited in claims 25-28, is definite and the rejection of claims 25-28 under 35 U.S.C. § 112, second paragraph, has been overcome and should be withdrawn.

IV. The rejection of claims 21-31 under 35 U.S.C. § 112, first paragraph, for lack of enablement, has been overcome

The Examiner rejected claims 21-31 under § 112, first paragraph, for asserted lack of enablement, acknowledging that the application enabled methods for producing BVDV subunit vaccines, but arguing that the application does not reasonably provide enablement for any subunit vaccine. Office Action at pages 3-4. Continuing, the Examiner acknowledges the presence of working examples, noting that the examples are limited to BVDV. *Id.* at page 4. The Examiner asserts, however, that there is no guidance for practicing the invention with

whole virus or bacterium, implicitly noting that such forms may be required, e.g., in eliciting an immune response to Hepatitis A virus. *Id.* The Examiner further notes that there are no known protective vaccines against HIV. *Id.* The Examiner concludes by asserting that undue experimentation would be required to use the full scope of the claimed subject matter and summarizes the support for the rejection by stating that "[w]ithout specific guidance or direction and/or working examples, one of ordinary skill in the art would not be able to reproducibly practice the entire scope of the invention as claimed, without undue experimentation." *Id.* at pages 4-5. In response, Applicant traverses.

As noted by the Examiner, a consideration of the eight Wands factors enumerated by the Examiner guides the inquiry into enablement. Although an exhaustive treatment of each factor may not be required in every instance, the Examiner considered only two of those eight factors, and Applicant respectfully submits that the Examiner's consideration of each of those factors was flawed. Accordingly, Applicant submits that the Examiner has failed to establish a *prima facie* case of non-enablement for any of rejected claims 21-31, and a consideration of each of the Wands factors confirms that conclusion.

The two Wands factors considered by the Examiner are the amount of guidance and whether working examples were provided or not. With respect to guidance, the Examiner stated that "[t]here is no guidance on how to practice the invention with whole virus or bacterium. There is no guidance on how to practice the invention all pathogens. It is well known in the art that Hepatitis A virus does not produce a protective immune response as a subunit, but only as a whole virus. There are no known protective vaccines against HIV." Office Action at pages 4-5. The claims, however, are not drawn to a method of using whole virus, bacterium or any other pathogenic organism in the methods for producing immunogenic complexes. Rather, the claims are drawn to methods of producing immunogenic complexes comprising an antigenic polypeptide and heat shock protein. The source of the antigenic polypeptide is a pathogenic organism such as a virus or bacterium, but the methods use the antigenic polypeptide of the organism, and are not dependent on the organism itself. Thus, the Examiner's assertion that Hepatitis A only produces a protective immune response when used as a whole virus and not as a subunit, is irrelevant. Further, although the Examiner has not asserted that Hepatitis A subunits would be immunogenically ineffective when found in association with heat shock proteins, the point is that the

immunogenicity of viral subunits, or whole viruses, is not relevant to the issue of whether the instant application teaches how to make and use immunogenic complexes comprising an antigenic polypeptide and heat shock protein. Accordingly, the Examiner's reliance on a lack of guidance in rejecting the claims has been misplaced. The antigenic polypeptides recited in the claims may be of any length, provided they are antigenic. The antigenicity of a polypeptide, moreover, could be readily determined by one of skill in the art using well-known, routine procedures employing conventional techniques. Additionally, the working examples disclose methods involving the use of parts of the E2, E0 and NS3 proteins of BVDV.

Provided with the information that the method requires an antigenic polypeptide and a non-mammalian cell to produce the non-mammalian heat shock protein/antigenic polypeptide complex, the skilled person would routinely be able to determine a range of polypeptides that may be used, so long as those polypeptides were antigenic. The examples provided would guide the skilled person in performing the steps used to generate a range of complexes, utilizing a range of antigenic polypeptides.

The Examiner suggests that the specification does not enable immunogenic complexes of hsps/HIV polypeptides that have a protective effect. The specification and claims are directed to the formation of an immunogenic complex between an hsps and an antigenic polypeptide. The Examiner has not asserted that there are no antigenic HIV polypeptides, and clinical data are available to rebut any such assertion. Rather, the Examiner has focused on problems with existing vaccine technologies for which the present invention provides a solution. The Examiner has not asserted that one of skill, aware of the disclosure in the present application, would be unable to produce an antigenic HIV polypeptide, or to form a complex with such an HIV polypeptide and hsps. Stated more generally, once an antigenic polypeptide is obtained, that polypeptide may be employed in the production method of the invention using no more than routine skill in view of the breadth of the teaching in the application.

In addition to misplaced reliance on a failure to provide sufficient guidance, the Examiner also considered the working examples as a Wands factor relevant to enablement. The basis for considering the working examples was the assertion that "[t]he working examples are drawn to BVDV" (Office Action at page 4), and the assertion that "[w]ithout

specific guidance or direction and/or working examples, one of ordinary skill in the art would not be able to reproducibly practice the entire scope of the invention as claimed, without undue experimentation." Office Action at page 5. The relevant Wands factor is whether working examples are present or not, and the Examiner has acknowledged their presence. *See* Office Action at page 4. Thus, this factor favors a finding that the claims are enabled. In the language quoted above, from page 5 of the Office Action, the Examiner cannot be effectively asserting "without working examples, . . ." because such an assertion is directly contradicted by the Examiner's acknowledgement of working examples and by the actual presence of working examples in the application as filed. To the extent that the Examiner is effectively asserting that "without specific working examples, . . ." the Examiner has adopted an improper standard for assessing enablement. There is no requirement to provide a working example of every embodiment falling within the scope of the claims. Stated alternatively, claims are not limited to the disclosed embodiments absent some limiting language in the claims. Accordingly, there is no legal requirement for "specific" working examples. What is relevant to a consideration of enablement is the presence or absence of working examples, and there is no question about the presence of working examples in the instant case.

For all of the foregoing reasons, Applicant submits that the Examiner has failed to establish a *prima facie* case of non-enablement for any of claims 21-31 and the rejection should therefore be withdrawn.

A consideration of the remaining Wands factors confirms that each of pending claims 21-31 is enabled throughout its full scope. The nature of the invention is immunogenic complexes, which have been known in a variety of forms for many years. The subject matter at issue in Wands itself was immunogenic material, and those claims were held to be enabled. The state of the prior art was well developed in terms of identifying and/or obtaining a variety of antigenic polypeptides, as well as antigenic fragments and antigenic derivatives thereof. The techniques needed to identify and obtain such polypeptides were well known in the art, and the Examiner has not challenged that fact. In addition, heat shock proteins were known in the art. Provided with the teachings in the instant application, coupling an antigenic polypeptide and hsps in an immunogenic complex would have required nothing more than routine skill. The factor relating to predictability of the art of immunogenic complexes also

favors a conclusion that the claims were enabled. As noted by the Wands court, the immunological arts are predictable in that an experiment in which a quantity of antigen is exposed to cells of the immune system leads to the predictable outcome of an antigenic response, or antibody, being elicited. The present facts are analogous to the facts at issue in Wands and lead to the conclusion that the art of exposing a complex containing an antigenic polypeptide and hsps to an immune system cell will typically elicit an immunological response. Thus, the relevant art is predictable. With respect to the amount of guidance presented, the application provides thorough guidance in obtaining antigenic polypeptides from pathogenic organisms and in obtaining hsps. As taught in the application, these molecules associate, or couple, intracellularly and are readily recoverable using conventional techniques to provide the immunogenic complexes in a form suitable for use as a vaccine. The Examiner's comments regarding guidance for generating immunogenic complexes containing whole viruses is not relevant to an assessment of the guidance regarding immunogenic complexes formed of antigenic polypeptides and hsps that is provided by the application. Another factor is the quantity of experimentation. As taught in Wands, exposure of immune system cells to a quantity of antigen followed by numerous parallel screens for immunogenic reactions is interpretable as a single experiment. Analogously, identifying or obtaining antigenic polypeptides from pathogenic organisms may involve no more than one experiment. The remaining activities required to make and use the claimed methods, i.e., obtaining the encoding nucleic acid, expressing it in non-mammalian cells induced to express hsps, and recovering the complexes produced therein, involve conventional techniques and an insubstantial quantity of routine experimentation. Thus, the quantity of experimentation also supports a conclusion favoring enablement. With respect to the level of skill in the art, the courts have recognized a high level of skill in the immunological arts. Finally, the breadth of the claims is tailored to the inventive contribution, i.e., that antigenic polypeptides of pathogenic organisms can be coupled to hsps to yield usefully immunogenic complexes suitable, e.g., as vaccines.

Based on the foregoing analysis, Applicant submits that the Examiner has not established, and cannot establish, a *prima facie* case of non-enablement for any of rejected claims 21-31 under 35 U.S.C. § 112, first paragraph, for asserted lack of enablement and, therefore, the rejection has been overcome and should be withdrawn.

V. The rejection of claims 21-24 and 29-31 under 35 U.S.C. § 102(b) over Srivastava has been overcome

The Examiner rejected claims 21-24 and 29-31 under § 102(b) over Srivastava, asserting that the reference taught a method of making an immunogenic complex comprising HSP and heterologous antigenic peptides in insect cells. Further, the Examiner argued that the potentially distinguishing step of providing a stimulus to a cell to induce hsp production was not disclosed in the instant application as resulting in production of a distinguishable product. The Examiner then shifts the burden to Applicant to distinguish the claimed product from the prior art product. In response, Applicant traverses.

A rejection under § 102(b) requires that a single prior art reference disclose each and every limitation of the claimed subject matter. Srivastava does not disclose each limitation of any of claims 21-24 or 29-31. In fact, Srivastava is distinguishable from the claimed subject matter in several respects. First, Srivastava does not disclose non-mammalian hsps. Second, Srivastava does not disclose hsps in non-mammalian cells. *See* claims 21-24 and 29-31, as amended herein. Rather, Srivastava disclosed mammalian hsps from mammalian cells. *See, e.g.*, Srivastava at page 17, lines 9-24 (hsps principally of human origin), page 18, lines 29-33 ("the recombinant hsp produced in the host cell or library cell is of the same species as the intended recipient of the immunogenic composition. Recombinant hsp is most preferred"), page 28, lines 4-7 ("the host cells are the same species as a patient to whom the hsp-peptide complexes are subsequently administered"), Section 5.2 (describing hsp-peptide complexes from "any mammalian cells, for example, human cells"), and the Example, wherein only the preparation of hsp-peptide complexes in human cells is described).

Additionally, intracellular production of hsps of the claimed methods are induced, e.g., by stressing, in the non-mammalian cells. For example, the non-mammalian cells are exposed to heating to provide stress and induce hsps production therein. In contrast, Srivastava does not induce hsps, for example by stressing the host cells with heat. Yet another distinction is the use of native hsps in the claimed methods, whereas Srivastava taught the use of recombinant hsps.

The distinctions between the disclosure of Srivastava and the claimed methods establish that the reference fails to disclose, expressly or implicitly, (1) the non-mammalian hsps and (2) the non-mammalian cells of the claims. Moreover, these distinctions are

patentably significant. An immunogenic complex comprising non-mammalian hsp produced in a non-mammalian cell would be expected to be perceived by mammalian organisms as foreign, thereby contributing, with the antigenic polypeptide, to the immunogenic property of the complex in mammalian organisms. For these reasons, Applicant submits that Srivastava does not anticipate the subject matter of any one of claims 21-24 or 29-31 under 35 U.S.C. § 102(b); the rejection has therefore been overcome and should be withdrawn.

VI. The rejection of claims 21 and 25-28 under 35 U.S.C. § 103(a) over Srivastava in view of Deregt has been overcome

The Examiner rejected claims 21 and 25-28 as obvious under § 103(a) over Srivastava in view of Deregt, asserting in support that Srivastava teaches the making of immunogenic complexes with HSPs and Deregt teaches that both BVDV is a known pathogen of bovines and that the E2 region has been used as a subunit vaccine. Motivation for combining the teachings was assertedly found in Srivastava's teaching that the immunogenic complexes give rise to immune responses, thereby providing motivation to make other immunogenic formulations, and BVDV was a known pathogen of a domesticated commercial animal, the cow. A reasonable expectation of success was found in Deregt's teaching that administration of the E2 region of BVDV gave rise to neutralizing antibodies. In response, Applicant traverses.

Srivastava, the primary reference, was shown above to lack any disclosure related to (1) the use of non-mammalian hsps, or (2) the use of non-mammalian cells. Moreover, Srivastava does not even suggest the use of either non-mammalian hsps or non-mammalian cells. Each of these features is a limitation in each of rejected claims 21 and 25-28, as effectively amended. These defects in the disclosure of Srivastava are not remedied by the disclosure of Deregt, which discloses the use of the E2 region of BVDV in an effort to produce vaccines, with equivocal results. Importantly, Deregt does not disclose or suggest either non-mammalian hsps or non-mammalian cells used to produce immunogenic complexes. Thus, Srivastava and Deregt, considered individually or in combination, fail to disclose or suggest each limitation of any one of the rejected claims, a requirement for establishing a *prima facie* case of obviousness for claimed subject matter. Accordingly, the Examiner has failed to establish a *prima facie* case of obviousness for the subject matter of any of the rejected claims. Moreover, the noted differences between the cited references and

the claimed subject matter provide a patentable distinction in that non-mammalian hsps and cells would produce immunogenic complexes better suited for use as vaccines in all mammals, in comparison to complexes containing mammalian hsps or produced in mammalian cells. For this reason alone, Applicant submits that a *prima facie* case of obviousness of claims 21 and 25-28 under 35 USC §103(a) over Srivistava in view of Deregt has not been, and cannot be, established. Accordingly, the rejection has been overcome and should be withdrawn.

Deregt discloses that a number of groups had previously used recombinant E2 antigens in vaccines to immunize cattle, sheep or pigs and that E2 has neutralizing domains which can be recognized by antibodies. Although Deregt pointed out that a number of studies had been carried out using sub-unit vaccines against pestiviruses, all of these references showed that the approach did not work in studies carried out in ruminants such as cows and sheep.

Animals vaccinated with E2 antigens were then challenged with similar live pestiviruses to the derived E2 immunogenic proteins used in the vaccines. As Deregt states, "its use as a component of subunit vaccines for BVDV in cattle and sheep, and CSFV in swine, have demonstrated that varying levels of protection against disease can be achieved by vaccination with E2." In fact, in three of the four reported studies, (all carried out in cattle and sheep), the levels of protection were very low, below a protection that would be acceptable for a commercial vaccine.

The only previously published study showing any real level of recombinant E2-only protection was that carried out in pigs by van Rijn *et al.* (1996). Here, E2 derived from one CSFV isolate was used in a vaccine that gave protection only against lethal challenge with the same live CSFV isolate (Brescia). Protection was based only on the development of homologous neutralizing antibodies in pigs and there was no measurement of fetal protection, as carried out in the present application.

Where fetal protection studies were carried out in sheep (e.g., in Bruschke *et al.* (1997)), there was incomplete protection even against homologous challenge. That is, the same live virus was used to challenge the vaccinated sheep as the recombinant E2 protein used in the vaccine. In contrast, the hsps/antigenic polypeptide complex of the present

claims, when used for the vaccination of cattle, gave 100% protection against BVDV infection in the fetuses of vaccinated animals.

Furthermore, in the experiments reported in the present application, it is apparent that not only was a combination of E2 proteins used, but two E0 proteins and a single NS3 protein were combined as well. All of these immunogenic fragments were coupled *in vivo* with heterologous hsps, and the immunized animals withstood challenge with a heterologous live BVDV isolate. Therefore, the present application did not use just E2 proteins, as in previous studies, and the immunized animals were subjected to a far more severe test than any previously reported pestivirus antigen trial conducted in any animal.

Perhaps most importantly, in none of the studies reported prior to the filing of the present application was there any mention made of using heat shock proteins in any form to enhance the recombinant E2 antigens used with conventional adjuvants.

As discussed above, Srivastava does not teach the induction of hsps/antigen complexes by stressing a cell to produce a native hsps which will naurally complex with the antigenic polypeptide *in situ* within the cell. Moreover, Srivastava does not disclose or suggest non-mammalian cells being used to generate hsps. Furthermore, Srivastava teaches that cell-mediated immunity (specifically, cytotoxic T lymphocyte-, or CTL-, mediated immunity) rather than antibodies (*see, e.g.,* Section 5.3 looking at the immunogenicity of hsps/antigen fusions only in the context of assaying for CTL activity and, although it does mention MLRs, these are again related to cell-mediated immunity). In addition, Srivastava would have taught anyone skilled in the art who did combine its disclosure with the previous disclosures of research on subunit vaccines that they would have to use recombinant mammalian (more specifically, bovine) hsps coupled in a separate system to just the E2 subunit pestivirus protein.

There would be no motivation for the skilled person to take the teachings of Deregt, which include the teaching that E2 is not an effective antigen for vaccination (and which does not suggest further proteins such as E0 and NS3 at all), and combine this with the teachings of Srivastava, which does not mention the induction of complexes of native hsps/antigen in a non-mammalian cell, to arrive at the method of producing the immunogenic complexes provided in the present application. Furthermore, as Deregt teaches an antibody-based technology, and Srivastava teaches a CTL-based technology, one of skill in the art would not

have combined these two distinct technologies from non-analogous arts, as experts in those arts would have believed that antibodies and CTLs are mutually opposed in their actions (that is, a Th1 versus a Th2 immune response).

For all of the foregoing reasons, Applicant submits that the Examiner has not established a *prima facie* case of obviousness for any of claims 21 or 25-28 under 35 U.S.C. § 103(a) over Srivastava in view of Deregt. Accordingly the rejection of claims 21 and 25-28 under § 103(a) over Srivastava in view of Deregt has been overcome and should be withdrawn.

The Examiner is invited to contact the undersigned at the telephone number listed below in order to discuss any remaining issues or matters of form that will move this case to allowance.

Dated: June 15, 2005

Respectfully submitted,

By _____

William K. Merkel
Registration No.: 40,725
MARSHALL, GERSTEIN & BORUN LLP
233 S. Wacker Drive, Suite 6300
Sears Tower
Chicago, Illinois 60606-6357
(312) 474-6300
Attorney for Applicant